I/II trial to determine the safety and efficacy of a combination of arsenic trioxide, melphalan and ascorbic acid (AA) as preparative regimen in patients undergoing high-dose therapy (HDT) and autologous hematopoietic progenitor cell transplantation for multiple myeloma (MM). We also assessed the impact ATO levels on melphalan pharmacokinetics (PK), engraftment and toxicity.

Methods: Forty-eight patients with secretory myeloma (23 females, 25 males; median age: 54, range: 35-70) were treated between 4/04 and 8/05. All patient received melphalan 100 mg/m2 IV on days -4 and -3 and AA 1000 mg/day IV on days -9 to -3. Patients were randomized to 3 arms; no ATO (arm 1), ATO 0.15 mg/kg IV on days -9 to -3 (arm 2) and ATO 0.25 mg/kg IV on days -9 to -3 (arm 3). Twelve patients had a prior autograft. Median CD34 cells dose infused was 4.5×10^6/kg (range 2.3 -10.9).

Results: Patients in all 3 arms were evenly matched. With a median F/U of 17 months (range 6-29) post autograft, no dose-limiting toxicity or non-relapse mortality was seen. Toxicity was limited to grade I or II nausea, vomiting and diarrhea and was similar in all 3 arms. Melphalan PK was not altered by ATO pretreatment. Median time to neutrophil engraftment (ANC >500/ dl) was 9 days, with no engraftment failures or delays in the ATO arms. CR rate for the entire group was 23%, and overall response rate (ORR=CR + PR) was 75%. Progression-free survival (PFS) and overall survival (OS) after 17-month F/U were 68% and 82%, respectively. There was no significant difference in CR, ORR, PFS or OS between the 3 arms (p = 0.9, 0.9, 0.5 and 0.6, respectively). A prior autologous transplant (p = 0.02) and abnormal cytogenetics at transplant (p = 0.04) were associated with a significantly shorter remission.

Conclusions: ATO + melphalan + ascorbic acid is a safe, effective and well tolerated preparative regimen for patients with multiple myeloma undergoing an autotransplant. A prior autograft and abnormal cytogenetics are associated with worse outcome.

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AUTOLOGOUS STEM CELL TRANSPLANTATION FOR ELDERLY PATIENTS WITH MULTIPLE MYELOMA

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Background: Several trials have shown that autologous stem cell transplantation is superior to conventional therapy in terms of complete response (CR) rate, event-free survival (EFS) and overall survival (OS). This treatment, however, is generally limited to patients younger than 65 due to concerns about excessive toxicity and treatment-related mortality (TRM) in older patients. Previous reports have shown that age alone should not exclude patients from high-dose therapy, as long as they fulfill other eligibility criteria. In this report we analyzed the safety and efficacy of high-dose chemotherapy (HDT) and autologous transplant in patients with MM who were ≥ 70 years at the time of autotransplant.

Methods: Twenty-six patients (16 males, 10 females) with a median age of 72 (range 70-79) underwent HDT and an autograft between July 1999 and October 2005. The preparative regimen was melphalan 200 mg/m2 in 19 patients (73%), melphalan 180 mg/m2 in 6 and melphalan140 mg/m2 in 1 patient. Of the 26 patients, 12 were receiving first remission consolidation, 7 had primary refractory disease and 7 had relapsed disease. Clonal cytogenetic abnormalities were present in 5 patients (19%).

Results: Twenty-two of the 26 patients were alive after a median follow up of 25 months (range 8-74). Responses (complete + partial response) were seen in 20 patients (77%), five (19%) of which were complete responses. Median PFS was 24 months and median OS has not been reached yet. 100-day TRM was 0%. Median times to absolute neutrophil count of $\geq 0.5 \times 109$/l and platelets $\geq 20 \times 109$/l were 10 and 10 days, respectively. Three-year PFS and OS were 39% and 65%, respectively. A serum albumin <3.5 g/dl (p=0.02), abnormal cytogenetics at transplant (p=0.05) and >2 prior chemotherapy regimens (p=0.02) were associated with a shorter PFS. Patients transplanted with relapsed disease had a shorter OS (p=0.0004). ISS stage, β2 microglobulin level, lactic dehydrogenase (LDH) level, abnormal cytogenetics, CCI or HCT-CI at the time of transplant did not emerge as significant predictors of PFS or OS in this group of patients.

Conclusions: HDT and autologous transplant is safe and feasible in selected patients ≥70 years of age. Patients transplanted with relapsed disease had a shorter OS.

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TOTAL MARROW IRRADIATION (TMI) USING HELICAL TOMOTHERAPY: DOSIMETRIC ANALYSIS DEMONSTRATES REDUCED ORGAN DOSES WHICH CORRELATE WITH REDUCTION IN ACUTE TOXICITIES AND PREDICT FOR ESCALATION OF DOSE TO TARGET MARROW BEYOND THAT ACHIEVABLE BY STANDARD TBI

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TBI dose escalation has been difficult due to associated organ toxicities. We recently demonstrated the feasibility of using Tomotherapy (an image guided IMRT delivery system) to deliver a more targeted dose of TBI to sites of greatest tumor burden (bone/marrow) with reduced dose to normal organs in a patient with multiple myeloma. This study provides a dosimetric analysis of target bone/marrow and normal organ doses from the first 13 patients treated, and details of set-up and delivery using this novel system.

Twelve patients with multiple myeloma (MM) were treated with Mel (200 mg/m^2) followed 6 weeks later by TMI as part of a tandem autologous transplant Phase I/II trial. Total TMI doses were 10 Gy (3 patients), 12 Gy (4 patients), 14 Gy (3 patients) and 16 Gy (2 patients) delivered 2 Gy QD or BID over 5 days. One patient with AML was treated with TMI+TLI to 12 Gy (1.5 Gy BID) + concomitant Flu/Mel on a separate trial. Treatment time was 50 minutes, jaw size 2.5 cm, and pitch 0.45. Patients were treated supine with full body immobilization. Whole body CT imaging was performed by the Tomotherapy unit prior to each fraction to provide 3D alignment of patient anatomy to the intended target regions.

Median organ doses ranged from 15-65% that of the target bone/marrow dose. The degree of organ sparing was similar for all patients despite differences in thickness and habitus. Of the 84 TMI treatment sessions delivered, only one was temporarily interrupted due to nausea and vomiting. In the immediate post-TMI period, all MM patients experienced grade 1-2 nausea, with half experiencing no vomiting. Erythema, diarrhea, and mucositis were infrequent and grade 1-2. The AML patient experienced grade 2 nausea, grade 1 vomiting and grade 3 mucositis. This compares favorably to acute symptoms associated with large field hemibody RT or standard TBI.

This study confirms the feasibility of using Tomotherapy to deliver TMI. Dosimetric studies demonstrated reduced organ doses and predicted for reduced toxicities. Clinical results confirmed these predictions. The techniques used can be adapted by most centers with the technology. This study predicts for the ability to dose escalate to a level where normal organs receive comparable standard TBI doses with target regions receiving a significantly higher dose than achievable with TBI, offering the potential for improved outcomes in patients with hematologic malignancies.

GRAFT PROCESSING

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EX-VIVO EXPANSION (EvE) OF PREVIOUSLY CRYOPRESERVED CORD BLOOD (CB) INTO NATURAL KILLER (NK) CELLS WITH ENHANCED AML AND NEUROBLASTOMA CYTOTOXICITY: POTENTIAL ROLE OF CB NK CELLS IN ADOPTIVE CELLULAR IMMUNOTHERAPY (ACI)

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CD56$^+$ NK subsets exhibit differential NK receptors (NKR) such as cytotoxicity profiles including killer-Ig-like receptors (KIR), C-lectin (NKG2) and natural cytotoxicity receptors (NCR)